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ORIGINAL INVESTIGATION

Divergent effects of D_{2/3} receptor activation in the nucleus accumbens core and shell on impulsivity and locomotor activity in high and low impulsive rats

M. Moreno · D. Economidou · A. C. Mar ·
C. López-Granero · D. Caprioli · D. E. Theobald ·
A. Fernando · A. H. Newman · T. W. Robbins ·
Jeffrey W. Dalley

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Abstract

Rationale Previously we demonstrated reduced D_{2/3} receptor availability in the ventral striatum of hyper-impulsive rats on the five-choice serial reaction time task (5-CSRTT). However, the anatomical locus of D_{2/3} receptor dysfunction in high impulsive (HI) rats is unknown.

Objective In the present study, we investigated whether D_{2/3} receptor dysfunction in HI rats is localised to the core or shell sub-regions of the nucleus accumbens (NAcb).

D. Economidou deceased.

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M. Moreno · C. López-Granero
Department of Psychology, University of Almeria,
Almeria, Spain

D. Economidou · A. C. Mar · D. Caprioli · D. E. Theobald ·
A. Fernando · T. W. Robbins · J. W. Dalley
Behavioural and Clinical Neuroscience Institute,
University of Cambridge, Cambridge, UK

D. Economidou · A. C. Mar · D. Caprioli · D. E. Theobald ·
A. Fernando · T. W. Robbins · J. W. Dalley (✉)
Department of Psychology, University of Cambridge, Downing St,
Cambridge CB2 3EB, UK
e-mail: jwd20@cam.ac.uk

A. H. Newman
Medicinal Chemistry Section, National Institute on Drug
Abuse—Intramural Research Program,
National Institutes of Health, Baltimore, MD, USA

J. W. Dalley
Department of Psychiatry, University of Cambridge,
Cambridge CB2 2QQ, UK

Methods Rats were selected for low (low impulsive, LI) and high impulsivity on the 5-CSRTT and implanted with guide cannulae targeting the NAcb core and shell. The D_{2/3} receptor agonist quinpirole was locally injected in the NAcb (0.1, 0.3 and 1 µg per infusion) and its effects investigated on the performance of LI and HI rats on the 5-CSRTT as well as spontaneous locomotor activity in an open field.

Results Intra-NAcb core quinpirole increased premature responding in HI rats but not in LI rats. In contrast, intra-NAcb shell quinpirole strongly increased locomotor activity in HI rats, unlike LI rats. This effect was blocked by intra-NAcb shell infusions of the D_{2/3} receptor antagonist nafadotride (0.03 µg). However, nafadotride was ineffective in blocking the effects of intra-NAcb core quinpirole on premature responding in HI rats.

Conclusions These findings indicate that impulsivity and hyperactivity are separately regulated by core and shell sub-regions of the NAcb and that HI rats show an enhanced response to D_{2/3} receptor activation in these regions. These results suggest that the symptom clusters of hyperactivity and impulsivity in attention-deficit hyperactivity disorder may be neurally dissociable at the level of the NAcb.

Keywords Impulsivity · Locomotion · Quinpirole · Nafadotride · Dopamine · Nucleus accumbens

Introduction

A number of psychopathological disorders including obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), schizophrenia and drug abuse are associated with high levels of impulsivity (American Psychiatric Association 2000).

Preclinical and clinical studies demonstrate that high impulsivity and its related psychopathological disorders involve a dysregulation of the brain dopamine (DA) systems (Dalley et al. 2011; Fineberg et al. 2010; Volkow et al. 2009).

Trait-like impulsivity in rats, as defined by spontaneously high levels of anticipatory responses made on a sustained visual attention test, the five-choice serial reaction time task (5-CSRTT) (Dalley et al. 2007; Robinson et al. 2009), predicts increased vulnerability to the reinforcing effects of psychostimulant drugs that target the mesolimbic DA system. High impulsive (HI) rats show greater escalation of cocaine and nicotine self-administration (Dalley et al. 2007; Diergaarde et al. 2008), and an increased propensity to develop compulsive cocaine-seeking and relapse compared with low impulsive (LI) rats (Belin et al. 2008; Economidou et al. 2009). Since HI rats exhibit a reduced availability of $D_{2/3}$ receptors in the ventral striatum, including the nucleus accumbens (NAcb), $D_{2/3}$ receptor dysfunction in the NAcb may be a marker of individual vulnerability to drug addiction (Dalley et al. 2011).

However, the decrease in $D_{2/3}$ receptor availability in the ventral striatum of HI rats could involve changes in one or more of the functionally distinct sub-regions of the NAcb, the NAcb core (NAcbC) and the NAcb shell (NAcbS). Previous research has strongly implicated the NAcbC and NAcbS in impulsivity, potentially operating in a functionally opposed manner (Besson et al. 2010; Economidou et al. 2012; Sesia et al. 2008). The NAcbC plays a significant role in regulating response inhibition on the 5-CSRTT (Basar et al. 2010; Dalley et al. 2011), as well as delay-discounting impulsivity (Cardinal et al. 2001). Increments in impulsive responding on the 5-CSRTT induced by systemic administration of D-amphetamine depend on D_2 -like receptors in the NAcbC, and to a somewhat lesser extent the NAcbS (Pattij et al. 2007). Moreover, lesions of the NAcbC potentiate, whereas lesions of NAcbS attenuate, the effect of D-amphetamine to increase premature responding in the 5-CSRTT (Murphy et al. 2008). Consistent with these effects, deep brain stimulation of the NAcbC and NAcbS produces strongly opposing effects on impulsivity on the 5-CSRTT (Sesia et al. 2008) while nafadotride, a D_3 -preferring antagonist (Sautel et al. 1995), increases impulsivity in HI rats when infused in the NAcbS but decreases impulsivity when infused in the NAcbC (Besson et al. 2010).

In the present study, we sought to investigate the neural locus of $D_{2/3}$ receptor dysfunction in the NAcb of impulsive rats on the 5-CSRTT. This was achieved by microinjecting the full $D_{2/3}$ receptor agonist quinpirole directly into the NAcbS and NAcbC of LI and HI rats prior to behavioural performance on the 5-CSRTT. As a control behavioural procedure we also assessed spontaneous locomotor activity, which has been shown to depend on D_2 -like receptors in the

NAcbS (Swanson et al. 1997). The comparison of impulsivity and hyperactivity is also important in the modelling of ADHD as these behaviours have been linked in a common, ‘combined’ symptom cluster, but potentially represent independent entities.

Materials and methods

Subjects

The subjects were 96 male Lister-hooded rats (Charles River, UK), housed in groups of four under temperature-controlled conditions and a 12:12-h light–dark cycle (lights off at 0700 h). Rats weighing approximately 250 g at the start of training were maintained at 85 % of their free-feeding weight by restricting access to laboratory chow (Purina, UK) to approximately 18 g/day per rat. Water was provided ad libitum. All procedures were conducted in accordance with the requirements of the UK Animals (Scientific Procedures) Act of 1986.

Apparatus and training

Rats were trained in eight operant 5-CSRTT chambers (25×25×25 cm), controlled by WhiskerServer (version 2.8) and FiveChoice client software (version 2.6) (<http://www.whiskercontrol.com>), as described previously (Bari et al. 2008; Robbins 2002). Each daily session consisted of 100 discrete trials with stable performance being achieved after about 40 sessions. Rats initiated a trial by nose-poking into the magazine. After an inter-trial interval (ITI) of 5 s, a light at the rear of one of the apertures was presented randomly in one of the five apertures for a duration of 0.5 s. Responses in this aperture within a limited illumination period (the limited hold period) were recorded as correct responses and were rewarded by the delivery of a food pellet into the magazine (Noyes 45 mg dustless reward pellets, Sandown Scientific Ltd, UK). Responses in a non-illuminated hole (an ‘incorrect’ response), a failure to respond within the 5 s limited hold period (an ‘omission’) and responses in one of the apertures during the ITI (a ‘premature’ response) were also recorded and signalled by a time-out period where the house-light was switched off for 5 s. The stimulus duration was 30 s in the initial training sessions and was progressively reduced to the final duration used for testing (0.5 s), depending on the rats individual performance. Rats reached the criterion of stable pre-operative performance when they achieved ≥80 % accuracy with fewer than 20 % omissions. An average of 40 daily sessions, each consisting of approximately 100 trials and lasting 30 min was required to reach this criterion.

Following acquisition of the 5-CSRTT, rats were screened for impulsivity over a 3-week period using the

same procedure as described previously (Dalley et al. 2007). Animals were first tested on two consecutive days using a stimulus duration of 0.5 s and an ITI of 5 s. On day 3, animals were challenged with a long ITI where the delay from trial onset to stimulus presentation was increased to 7 s, a manipulation that increases the frequency of premature responses and which helps to differentiate between high and low impulsive rats on the 5-CSRTT (Dalley et al. 2007). On days 4 and 5, animals were re-tested with a stimulus duration of 0.5 s and an ITI of 5 s. This cycle of short and long ITI testing was repeated on two further occasions. The criterion for selecting HI rats was a mean level of premature responses greater than or equal to 50 on each of the long ITI sessions. The frequency of HI rats in different batches of Lister hooded rats is remarkably stable and varies between 8 and 14 %. Rats were trained in two squads, each comprising 48 rats. LI rats were selected from the two squads as the lowest ranked animals in terms of mean premature responses during the three long ITI sessions. This screening procedure yielded 11 HI rats and 10 LI rats, which were each then subdivided into two groups for the subsequent intra-NAcbS and intra-NAcbC infusion experiments.

Surgery

Subjects were anaesthetised with ketamine (Ketaset, 100 mg/kg, intraperitoneally (i.p.); Vet Drug, Bury St Edmunds, UK) and xylazine (Rompun, 10 mg/kg, i.p. Vet Drug), and secured in a stereotaxic frame with the incisor bar set at −3.3 mm relative to the intraural line in a flat skull position. Bilateral 22-gauge double-guide cannulae (Plastic One, Sevenoaks, UK) were bilaterally implanted above either the NAcbC or the NAcbS, according to the following stereotaxic anterior–posterior (AP), mediolateral (ML) and dorsoventral (DV) coordinates NAcbC: AP +1.7 mm, ML ±1.9 mm, DV −2.2 mm; NAcbS: AP +1.7 mm, ML ±0.75 mm, DV −2.0 mm. AP and ML coordinates were taken from bregma, DV coordinates from skull surface (Paxinos and Watson, 1998). Cannulae were secured to the skull with dental acrylic and stainless steel screws, and a wire stylet occluded the guide to maintain patency. After surgery, animals were housed individually and allowed 5–7 days recovery.

Intracerebral drug administration

For all experiments, drugs were administered according to a fully randomised Latin-square design and separated by a minimum of 72 h between drug challenge sessions. Experiments were separated by a 1-week washout period. Quinpirole hydrochloride (Sigma Chemical, St. Louis, MO, USA) was prepared in 0.9 % NaCl. Nafadotride (Tocris Cookson, Bristol, UK) was dissolved in 1 M HCl and 0.9 % NaCl. The final pH was adjusted to approximately 6

using 0.1 M NaOH. Drug solutions were frozen at −80 °C prior to use.

Rats received two habituation sessions to the microinfusion procedure. During the first habituation session, the injector was inserted through the guide cannula and left in place for 1 min. In the second habituation session, rats received one control vehicle infusion (0.9 % NaCl). Here, rats were gently restrained while the stylets were removed. Twenty-eight gauge bilateral injectors (Plastics One, Sevenoaks, UK), extending 4.5 mm (NAcbC) or 5 mm (NAcbS) beyond the length of the guide cannulae, were left in place for 1 min before each infusion (0.5 µl infused over 1 min). Injectors were left in place for 1 min to allow for diffusion of the drug into the surrounding tissue. The injector was then removed and the stylet replaced. Infusion studies were run in 3-day cycles, starting with a baseline session on day 1. On the following day, rats received a drug or vehicle infusion, 5 min before testing in the 5-CSRTT or the photocell activity cages. On the third day, animals were not tested and remained in their home cage.

Locomotor activity assessment

HI and LI rats were tested in Plexiglas activity cages (measuring 39×39×15 cm), equipped with photocell beams interfaced to a microcomputer (San Diego Instruments, US). Over two consecutive days, animals were habituated to the activity cages before the beginning of the infusion experiment. Animals were also habituated to the microinfusion procedure in the activity cages. During each test session, and following a 30-min period of habituation to the test cages, rats received drug infusions into either the NAcbC or NAcbS, before being returned to the activity cages. Locomotor activity was measured as the number of photocell beam breaks over a 30-min period following each drug infusion.

Experimental design

The behavioural effects of quinpirole were tested in LI and HI rats following its administration into either the NAcbC or the NAcbS, and also following the administration of the D_{2/3} receptor antagonist nafadotride.

Experiment 1: Performance on the 5-CSRTT following quinpirole administration in the NAcbC or NAcbS

Rats received infusions of vehicle or quinpirole (0.1, 0.3 or 1 µg per side) into the NAcbC or NAcbS, and were placed in the 5-CSRTT chamber. Doses of quinpirole were chosen on the basis of previous experiments in our laboratory shown to be pharmacologically active in this region (Pezze et al. 2007).

Experiment 2: Effects of intra-NAcb quinpirole on locomotor activity

Rats received infusions of vehicle or quinpirole (0.1, 0.3 or 1 µg per side) into the NAcbC or NAcbS, and were placed in the activity cages. The doses of quinpirole were chosen based on a pilot study and on previous studies (Gong et al. 1999; Swanson et al. 1997).

Experiment 3: Effects of intra-NAcbC nafadotride on quinpirole-induced impulsivity on the 5-CSRTT

Rats received a vehicle infusion (0.01 M phosphate-buffered saline, PBS) or nafadotride (0.03 µg per side) into the NAcbC, followed 3 min later by a second infusion of vehicle or quinpirole (1 µg per side). Rats were tested with an ITI of 5 s. One HI rat was removed from the study due to unstable performance. The doses of quinpirole and nafadotride were chosen according to the results of experiments 1 and 2, as well as a previous study (Besson et al. 2010).

Experiment 4: Effects of intra-NAcbS nafadotride on quinpirole-induced locomotor activity

Rats received one infusion of vehicle or nafadotride (0.03 µg per side) into the NAcbS, and then 3 min later a second infusion of vehicle or quinpirole (1 µg per side), before being placed in the activity cages. The doses of quinpirole and nafadotride were chosen according to the results in experiments 1 and 2, and previous studies (Barik and Beaufrepaire 1996; Canales and Iversen 2000).

Histological assessment

Following the completion of the experiments, subjects were anaesthetised with a lethal dose of sodium pentobarbitone (1.5 ml per rat, i.p., Doletal 200 mg/ml, Rhone-Merieux, Athens, USA) and perfused transcardially with 0.01 M PBS followed by 4 % paraformaldehyde. Brains were removed and postfixed in paraformaldehyde. Prior to being cut, the brains were transferred to 20 % sucrose in 0.2 M PBS and left overnight. Coronal sections were cut at 60 µm on a freezing microtome and stained with Cresyl Violet. Cannulae locations were verified under a light microscope and mapped onto standardised coronal sections of a rat brain stereotaxic atlas (Paxinos and Watson 1998).

Data analysis

Impulsivity screening

Behavioural data were analyzed using two-way repeated-measures analysis of variance (ANOVA), with one within

subject's factor "session" (11 levels) and one between subject's factor "group" (HI, LI). Experiments 1 and 2: The effects of intra-NAcb infusions of quinpirole on 5-CSRTT performance and locomotor activity in HI and LI rats were analysed by three-way repeated measures ANOVA, with one within subject's factor "group" (HI, LI) and two between subject's factors "NAcb sub-region" (core, shell) and "drug" (saline, 0.1, 0.3 or 1 µg). The data were further analysed with a two-way repeated-measures ANOVA with factors "NAcb sub-region" and "drug". Experiments 3 and 4: The effects of co-administered nafadotride and quinpirole were analysed using a three-way repeated measures ANOVA with within-subject's factors "quinpirole" (saline, 1 µg) and "nafadotride" (vehicle, 0.03 µg) and one between subject's factor "group" (HI, LI). Homogeneity of variance was confirmed by Levene's test. Post-hoc comparisons were made using a Duncan's *t* test. We also performed non-parametric analyses using Friedman's ANOVA. Post-hoc comparisons were made using Wilcoxon signed-rank (for unrelated samples) and Mann–Whitney sum-rank (for related samples) tests. All tests were evaluated against two-tailed probabilities. As the non-parametric tests did not alter the main conclusions of this study only parametric statistics are reported. Statistical significance was set at $p < 0.05$.

Results

Characterisation of high impulsivity on the 5-CSRTT

Figure 1 and Supplementary Table 1 shows the profile of behaviour of LI and HI rats on the 5-CSRTT. HI rats made more premature responses compared with LI rats (group: $F_{1,19} = 64.6$, $p < .0001$; session: $F_{10,190} = 56.2$, $p < .0001$; group \times session: $F_{10,190} = 14.3$, $p < .0001$). The increase in premature responding observed on days 1, 6 and 11

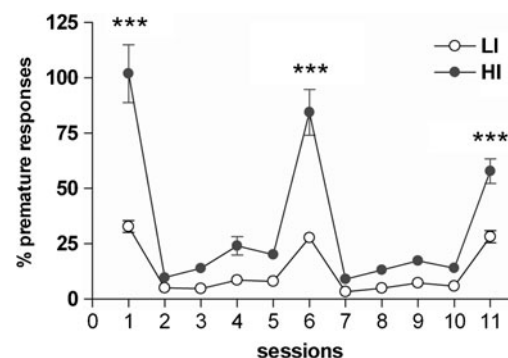


Fig. 1 Screening for impulsivity on the 5-CSRTT. Shown are levels of impulsivity, expressed as a percentage of premature responses, during baseline sessions (ITI = 5 s; sessions 2–5, 7–10) and long ITI sessions (LITI = 7 s; sessions 1, 6 and 11) in HI and LI rats. *** $p \leq 0.0001$ indicate significant differences vs LI on LITI sessions

coincided with the three challenge sessions (ITI of 7 s) used to screen for impulsivity. Post hoc analyses revealed that in the HI group, the challenge sessions produced a greater increase in premature responses on the 3 days tested ($p < 0.01$) compared to LI rats (Fig. 1). No significant differences were found between HI and LI on accuracy, omissions, perseveration, as well as correct and magazine response latencies (see [Supplementary Table 1](#)).

Figure 2 shows the positions of the injector tips in the NAcbC and NAcbS. In total, two rats were excluded from the study (one HI and one LI) because injector cannulae were positioned outside of the intended target areas. There was no gross tissue damage in the local vicinity of the injector tracks.

Experiment 1: Effects of intra-NAcbC and intra-NAcbS quinpirole on 5-CSRTT performance

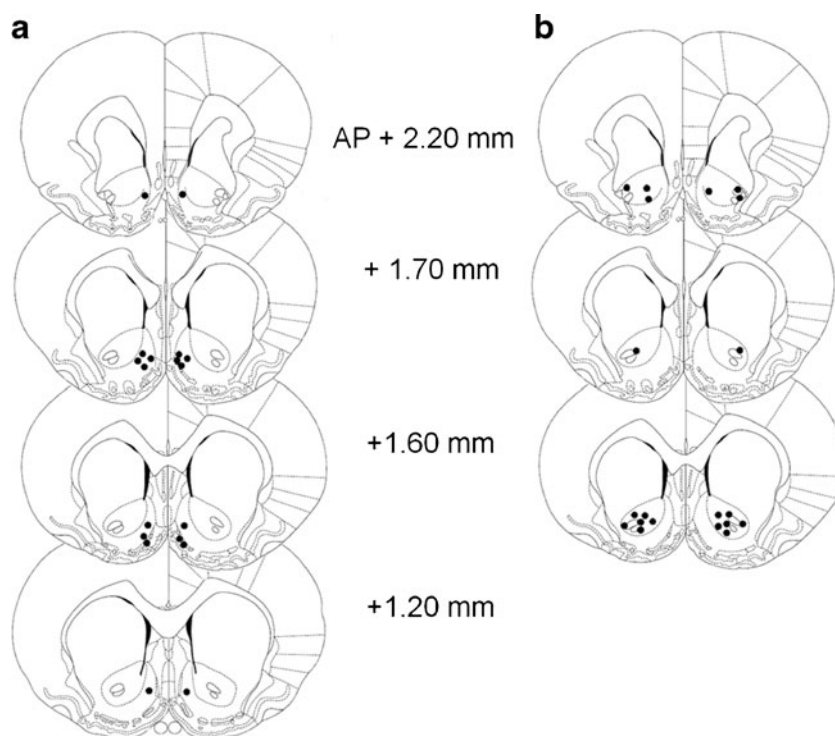
Figure 3 and Table 1 shows the effects of intra-NAcb quinpirole on premature responding and other behavioural measures on the 5-CSRTT. Quinpirole significantly increased impulsive responding in HI rats compared to LI rats (group \times drug: $F_{3,45}=6.2$, $p < 0.01$; group: $F_{1,15}=33.3$, $p < 0.001$; drug: $F_{3,45}=8.9$, $p < 0.001$). Divergent effects of quinpirole effects in HI and LI were also revealed by trend significant group \times drug \times NAcb sub-region interaction ($F_{3,45}=2.3$, $p = 0.09$) and a significant group \times NAcb sub-region interaction ($F_{1,15}=7.5$, $p < 0.05$; NAcb sub-region: $F_{1,15}=6.3$, $p < 0.05$). Further analyses confirmed that in HI rats (Fig. 3a),

quinpirole significantly increased impulsive responding, an effect that was dependent on NAcb sub-region (drug \times NAcb sub-region: $F_{3,24}=2.9$, $p < 0.05$; drug: $F_{3,24}=9.1$, $p < 0.001$). Post hoc analyses revealed that quinpirole significantly enhanced impulsive responding when infused into the NAcbC at the following doses: 0.1 μg ($p = 0.06$), 0.3 μg ($p < 0.001$) and 1 μg ($p < 0.001$) versus saline; and at 0.3 μg ($p < 0.01$) and 1 μg ($p < 0.001$) relative to same doses infused in the NAcbS. In contrast, quinpirole had no significant effect on premature responding in LI rats (Fig. 3b). There were no significant effects of intra-NAcbC or NAcbS quinpirole on accuracy, omissions, perseveration, correct response latencies and magazine latencies (see Table 1).

Experiment 2: Effects of intra-NAcbC and intra-NAcbS quinpirole on locomotor activity

Figure 4 shows the effects of intra-NAcb quinpirole on locomotor activity. Quinpirole produced a significant increase in locomotor activity with differential effects in HI and LI rats (group \times drug \times NAcb sub-region interaction: $F_{3,45}=3.2$, $p < 0.05$; drug: $F_{3,45}=19.1$, $p < 0.001$; NAcb sub-region: $F_{1,15}=4.4$, $p < 0.05$; group: $F_{1,15}=0.1$, $p = 0.4$). Further analyses confirmed that in HI rats (Fig. 4a), quinpirole significantly increased locomotor activity only when infused into the NAcbS sub-region (drug \times NAcb sub-region interaction: $F_{3,24}=5.9$, $p < 0.01$). Post hoc analyses revealed that quinpirole produced a dose-dependent increase in locomotor activity when infused into the NAcbS, at doses

Fig. 2 Schematic representations of the ventral-most position of injector tips in the NAcb shell (a) ($n=9$) and NAcb core (b) ($n=10$). Drawing adapted from Paxinos and Watson (1998)



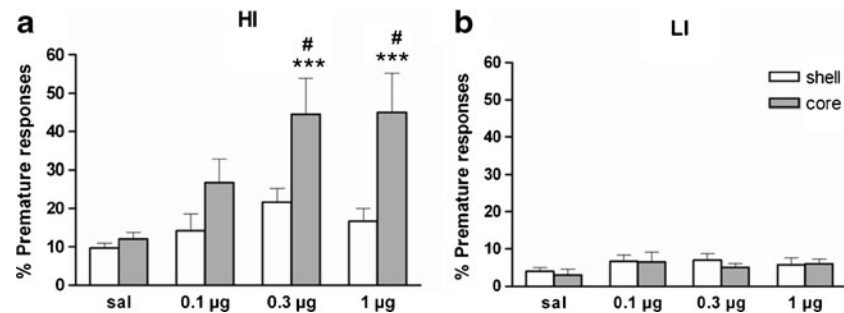


Fig. 3 Effects of microinfusions of the $D_{2/3}$ receptor agonist quinpirole (0.1, 0.3 or 1 μ g per side) into the NAcB (grey bars) and NAcS (white bars) of HI (a) and LI (b) rats on the 5-CSRTT. Final group sizes: NAcB (HI $n=5$, LI $n=5$); NAcS (HI $n=5$, LI $n=4$). Doses are

expressed as micrograms per 0.5 μ l. Data are means \pm SEM. *** $p \leq 0.001$ indicate significant differences vs saline infusion. # $p \leq 0.01$ significant differences vs same dose in NAcS

0.3 μ g ($p < 0.05$) and 1 μ g ($p < 0.001$) vs saline control group; and at 0.3 μ g ($p = 0.06$) and 1 μ g ($p < 0.001$) compared to the same doses in the NAcB. Thus, intra-NAcB quinpirole had no significant effect on locomotor activity in HI rats. However, in the LI rats (Fig. 4b), quinpirole increased locomotor activity when infused in the NAcB and the NAcS (drug effect: $F_{3,21} = 13.0$, $p < 0.01$). Post hoc analyses revealed that quinpirole significantly increased locomotor activity at the doses of 0.3 μ g ($p < 0.05$) and 1 μ g ($p < 0.0001$) relative to the saline group.

Experiment 3: Effect of intra-NAcB nafadotride on quinpirole-induced impulsivity

Figure 5 and Table 2 shows the effects of the intra-NAcB infusions of nafadotride in combination with quinpirole on impulsive responding and other behavioural measures on the 5-CSRTT. Quinpirole significantly increased impulsive responding in HI rats compared to LI rats (group \times drug: $F_{1,6} = 4.0$, $p < 0.05$). In the HI group (Fig. 5a), nafadotride (0.03 μ g) had no significant effect on premature responding,

Table 1 Effects of microinfusions of the $D_{2/3}$ receptor agonist quinpirole (0.1, 0.3 or 1 μ g per side) into the NAcB and NAcS of HI and LI rats on the 5-CSRTT

	Group	NAcB subregion	Sal	0.1 μ g	0.3 μ g	1 μ g
Accuracy (%)	HI	Shell	87.8 \pm 1.6	80.6 \pm 4.2	85.2 \pm 2.4	81.9 \pm 5.0
		Core	88.9 \pm 3.4	84.1 \pm 3.2	83.2 \pm 2.5	83.2 \pm 3.1
	LI	Shell	87.3 \pm 6.1	86.9 \pm 3.2	86.3 \pm 3.8	87.4 \pm 2.8
		Core	90.1 \pm 2.6	88.3 \pm 2.6	90.4 \pm 2.2	88.9 \pm 2.0
Omission (%)	HI	Shell	4.2 \pm 0.9	6.4 \pm 2.3	3.4 \pm 1.0	8.2 \pm 2.5
		Core	5.0 \pm 1.3	6.4 \pm 2.2	4.4 \pm 1.0	6.2 \pm 1.5
	LI	Shell	4.5 \pm 1.0	1.8 \pm 1.0	1.8 \pm 0.2	5.8 \pm 1.9
		Core	8.2 \pm 1.2	3.8 \pm 1.4	5.0 \pm 1.4	7.6 \pm 3.3
Perseveration	HI	Shell	39.6 \pm 5.90	50.4 \pm 8.10	46.0 \pm 6.4	63.2 \pm 10.5
		Core	64.4 \pm 11.5	65.6 \pm 13.9	66.8 \pm 14.0	61.2 \pm 11.5
	LI	Shell	56.3 \pm 12.0	38.8 \pm 13.9	45.3 \pm 19.9	50.5 \pm 22.4
		Core	60.4 \pm 13.0	51.2 \pm 12.0	58.2 \pm 16.5	61.2 \pm 27.4
Correct response latency (s)	HI	Shell	0.55 \pm 0.03	0.56 \pm 0.05	0.46 \pm 0.01	0.51 \pm 0.03
		Core	0.63 \pm 0.14	0.48 \pm 0.04	0.52 \pm 0.04	0.49 \pm 0.02
	LI	Shell	0.48 \pm 0.03	0.56 \pm 0.07	0.47 \pm 0.02	0.52 \pm 0.05
		Core	0.51 \pm 0.02	0.52 \pm 0.03	0.51 \pm 0.04	0.50 \pm 0.01
Magazine latency (s)	HI	Shell	1.69 \pm 0.11	1.68 \pm 0.22	1.59 \pm 0.15	2.19 \pm 0.69
		Core	1.50 \pm 0.11	1.33 \pm 0.10	1.38 \pm 0.97	1.48 \pm 0.11
	LI	Shell	2.33 \pm 0.57	2.41 \pm 0.69	1.61 \pm 0.38	1.87 \pm 0.27
		Core	1.95 \pm 0.38	3.06 \pm 1.45	1.61 \pm 0.13	1.55 \pm 0.17

Final group sizes: NAcB (HI $n=5$, LI $n=5$); NAcS (HI $n=5$, LI $n=4$). Doses are expressed as micrograms per 0.5 μ l. Data are means \pm SEM

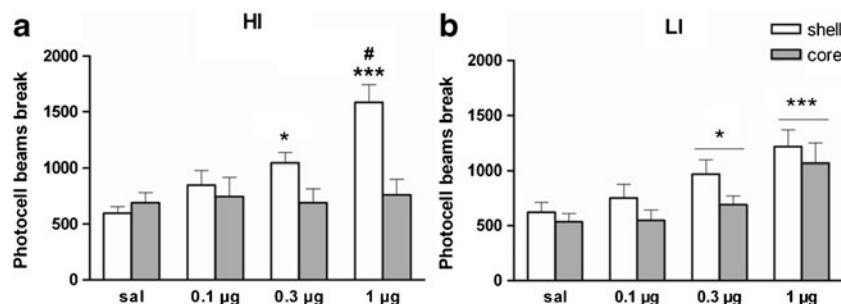


Fig. 4 Effects of microinfusions of quinpirole (0.1, 0.3 or 1 µg per side) into the NAcC (grey bars) and NAcS (white bars) of HI (a) and LI (b) rats on locomotor activity. Final group sizes: NAcC (HI $n=5$, LI $n=5$); NAcS (HI $n=5$, LI $n=4$). Doses are expressed as micrograms per

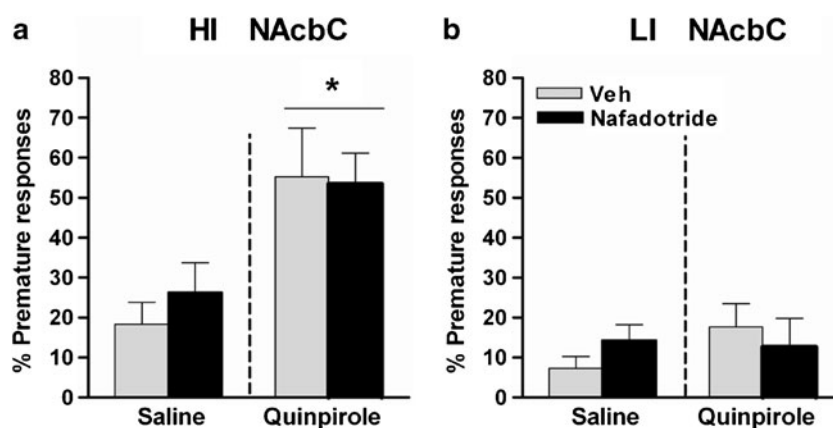
0.5 µl. Data are means \pm SEM. * $p \leq 0.05$ and *** $p \leq 0.001$ indicate significant differences vs saline infusion. # $p \leq 0.001$ significant differences vs same dose in NAcS

and did not block the enhancing effects of quinpirole on premature responding when infused into NAcC (quinpirole effect: $F_{1,4}=10.9$, $p < 0.05$). In the LI group (Fig. 5b), neither nafadotride nor quinpirole had any significant effect on premature responding.

Experiment 4: Effect of intra-NAcS nafadotride on quinpirole-induced locomotor activity

Figure 6 shows the effects of the intra-NAcS infusions of nafadotride in combination with quinpirole on locomotor activity. Nafadotride produced differential effects in HI and LI (group \times nafadotride \times quinpirole effect: $F_{1,7}=6.7$, $p < 0.05$). In the HI group (Fig. 6a), nafadotride blocked quinpirole-induced locomotor activity (quinpirole \times nafadotride interaction: $F_{1,4}=8.5$, $p < 0.05$). Post hoc tests revealed that intra-NAcS quinpirole increased locomotor activity ($p < 0.01$) vs saline; this effect was blocked when quinpirole was combined with nafadotride ($p < 0.01$, vs the vehicle-quinpirole group). In the LI group (Fig. 6b), quinpirole increased locomotor activity (quinpirole effect: $F_{1,3}=58.9$, $p < 0.01$); this effect was not blocked by nafadotride.

Fig. 5 Effects of intra-NAcC infusions of the D_3 receptor antagonist nafadotride (0.03 µg per side) on quinpirole-induced impulsivity on the 5-CSRTT (1 µg per side) in a HI rats ($n=5$) and b LI rats ($n=4$). Doses are expressed as micrograms per 0.5 µl. Data are means \pm SEM. * $p \leq 0.05$ indicate significant differences vs saline infusion



Discussion

The present study investigated $D_{2/3}$ receptor function in the core and shell sub-regions of the NAc associated with the presumed trait of high impulsivity in rats (Dalley et al. 2007). The main findings indicate a striking neuroanatomical dissociation in the effects of the $D_{2/3}$ receptor agonist quinpirole on impulsive responding in the 5-CSRTT and locomotor activity in low- and high-impulsive rats. We found that, while quinpirole exacerbated impulsivity in HI rats when infused in the NAcC, it had no effect on impulsivity in LI rats when administered into the NAcC or NAcS. Conversely, quinpirole produced locomotor hyperactivity in both HI and LI rats when infused into the NAcS but only in LI rats when infused into the NAcC. The stimulatory effect of quinpirole on locomotor activity however was greater in HI rats than LI rats. Overall, the double dissociation of behavioural effects according to NAc sub-regions indicates considerable specificity of function within the NAc and related structures, consistent with other recent evidence (e.g. Goto and Grace 2005; Reynolds and Berridge 2008). The pattern of findings also suggests that the effects

Table 2 Effects of intra-NAcbC infusions of the D₃ receptor antagonist nafadotride (0.03 µg per side) combined with quinpirole on the 5-CSRTT (1 µg per side) in HI rats (*n*=5) and LI rats (*n*=4)

	Group	Sal + Veh	N + Sal	Veh + Qui	Naf + Qui
Accuracy (%)	HI	74.3±6.2	77.8±3.0	71.8±8.7	79.0±3.0
	LI	82.9±3.9	85.1±5.9	84.4±4.5	74.2±2.5
Omission (%)	HI	8.4±3.1	4.3±0.8	9.5±3.1	4.6±2.0
	LI	8.7±2.8	2.75±1.4	4.5±1.0	10.7±6.7
Perseveration	HI	113.8±15.5	84.4±12.5	65.6±16.6	98.6±15.7
	LI	72.7±8.6	58.7±15.8	79.5±9.7	70.7±20.6
Correct response latency (s)	HI	0.63±0.13	0.61±0.05	0.73±0.23	0.67±0.10
	LI	0.57±0.01	0.57±0.07	0.54±0.03	0.62±0.06
Magazine latency (s)	HI	1.69±0.15	1.61±0.06	2.46±0.77	1.81±0.08
	LI	1.46±0.19	1.75±0.52	1.57±0.16	1.96±0.46

Doses are expressed as micrograms per 0.5 µl. Data are means ± SEM

of centrally infused quinpirole were quite well localised and unlikely to have arisen from diffusion to distal anatomical sites.

Our findings indicate that HI rats show an increased sensitivity to local D_{2/3} receptor stimulation in the NAcb, expressed as either hyperactivity or impulsivity depending on the precise sub-region of the NAcb affected. The results are not only important in revealing likely D_{2/3} receptor dysfunction in HI rats but also in demonstrating apparently independent neuroanatomical substrates for two key symptoms of ADHD at the level of the NAcb sub-regions, hyperactivity and impulsivity. The functional significance of this behavioural dissociation presumably arises from a consideration of the predominant anatomical projections to the core and shell, from in particular, medial prefrontal and hippocampal sources (Goto and Grace 2005). Hypothetically, these projections respectively govern cognitive control over those response preparatory processes that are impaired in HI rats in the 5-CSRTT, as well as locomotor exploratory responses to the environmental context.

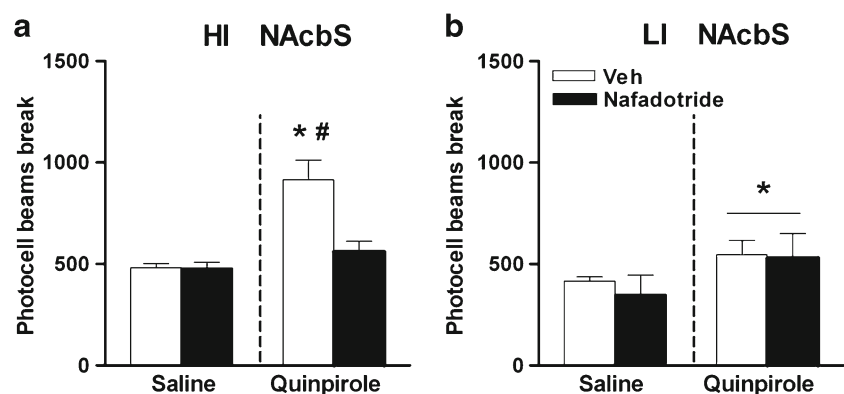
Neural basis of impulsivity

The present data add to accumulating evidence that impulsive responding on the 5-CSRTT is mediated by the NAcb

(Basar et al. 2010; Cole and Robbins 1989) probably via the core sub-region (Pattij et al. 2007). Thus the latter authors found that impulsive responding on the 5-CSRTT produced by D-amphetamine was blocked by intra-NAcbC infusion of the D_{2/3} receptor antagonists eticlopride or sulpiride. A similar blockade has been found following the induction of premature responses by lesions of the prefrontal cortex (Pezze et al. 2009). The relative lack of effect of quinpirole in LI rats is consistent with the evidence of Pezze et al. (2007) who similarly found that quinpirole did not increase premature responses in the 5-CSRTT.

Effects of nafadotride on hyperactivity and impulsivity

Intra-NAcb shell infusions of the D₃-preferring antagonist nafadotride blocked the effects of quinpirole on locomotor activity in HI rats but had no effect on increased impulsivity induced by local administration of quinpirole in the NAcbC. These findings are consistent with receptor binding studies that have highlighted the important role of D₃ receptors in the NAcbS, with relatively higher densities of D₃ than D₂ receptors as compared to the core sub-region (Bardo and Hammer 1991; Diaz et al. 1995, 2000). Although, the effects of other D₃ receptor antagonists on motor function are still controversial (Millan et al. 2000, 2004; Reavill et al.

Fig. 6 Effects of intra-NAcbS infusions of the D₃ receptor antagonist nafadotride (0.03 µg per side) on quinpirole-induced locomotor activity (1.0 µg per side) in **a** HI rats (*n*=5) and **b** LI rats (*n*=4). Doses are expressed as micrograms per 0.5 µl. Data are means ± SEM. ***p*≤0.01 indicate significant differences vs saline infusion. #*p*≤0.05 significant differences vs vehicle-quinpirole infusion

2000), previous studies have shown that intra-NAcb nafadotride, a preferential D_3 receptor antagonist, blocks hyperactivity induced by DA receptor agonists (Canales and Iversen 2000), supporting the role of D_3 receptors in the NAcb on hyperactivity.

In contrast, intra-NAcbC infusions of nafadotride were ineffective in blocking quinpirole-induced impulsive responding on the 5-CSRTT in HI rats. A previous study from our laboratory did show a reduction in impulsive responding by a higher dose of nafadotride (0.1 μ g) into NAcbC, but the same dose as used in the present study (0.03 μ g) did not affect impulsive responding on the 5-CSRTT in HI rats (Besson et al. 2010). Although nafadotride has been shown to be a preferential antagonist of D_3 receptors, possible actions at D_2 receptors cannot be discounted, especially at higher doses (Flietstra and Levant 1998). Therefore, the lack of effect of intra-NAcbC nafadotride on impulsivity in HI rats suggests that the effects of quinpirole on impulsivity in this region may be mediated by D_2 receptors. Indeed, it has been previously been demonstrated that amphetamine-induced impulsivity is more effectively blocked by D_2 receptor antagonists than selective D_3 receptor antagonists (van Gaalen et al. 2009). In addition to finding reductions in impulsive responding following high doses of intra-core nafadotride, Besson et al. (2010) reported an increase in impulsivity when nafadotride was infused in the NAcbS of HI rats—supporting (1) the hypothesis that $D_{2/3}$ receptors in the core mediate impulsive behaviour, and (2) a possible ‘opponent’ effect on impulsivity of DA acting at D_3 receptors in the shell sub-region.

Differential effects of quinpirole in low- and high-impulsive rats

Previously, it was found that systemic quinpirole dose-dependently and selectively reduced impulsive responding in HI rats on the 5-CSRTT (Fernando et al. 2012), whereas the present results following central administration show only dose-dependent increases in responding. It would therefore appear likely that the site of the impulsivity-reducing effects is not in the NAcb, other obvious sites possibly including the ventral tegmental area, dorsal striatum or prefrontal cortex. Indeed, infusion of quinpirole into the orbitofrontal cortex of HI rats has been shown to decrease premature responding on the 5-CSRTT, but it also affected other performance parameters such as a reduction on accuracy, increased omissions and latencies to respond, suggesting more general, non-specific actions at this site (Winstanley et al. 2010).

We previously reported that impulsivity in rats is inversely related to the availability of $D_{2/3}$ receptors in the ventral striatum, including the NAcb (Dalley et al. 2007). The present study was partly motivated by the relatively poor

spatial resolution of positron emission tomography used in our earlier study, which was unable to localise changes in $D_{2/3}$ receptors to the principal sub-regions of the NAcb. We hypothesised that HI rats would show altered behavioural responses to a $D_{2/3}$ receptor agonist locally administered in the NAcb core and shell. In fact, impulsivity was exacerbated in HI rats when quinpirole was locally administered in the NAcbC and HI rats were also more hyperactive than LI rats when quinpirole was administered in the NAcbS. These results thus indicate an important neural dissociation in the modulation of hyperactivity and impulsivity across the two sub-divisions of the NAcb, possibly differentially dependent on D_2 and D_3 receptors. They are consistent with other recent findings of an apparent opponent modulation of these behaviours by DA and noradrenergic mechanisms between the NAcb sub-regions (Economidou et al. 2012). Furthermore, the results suggest that increased DA transmission in the NAcbC is sufficient to increase impulsivity on the 5-CSRTT but only in animals showing spontaneously high levels of impulsive behaviour. These effects were behaviourally selective, with no effects for example, on other parameters of 5-CSRTT performance, including attentional accuracy.

A putative mechanism to account for such behavioural hyper-responsiveness, in the absence of any strong evidence of presynaptic DA dysfunction in HI rats (Dalley et al. 2007), would be post-synaptic receptor supersensitivity. However, this is inconsistent with the evidence of reduced $D_{2/3}$ receptor number, as measured with PET (Dalley et al. 2007) unless there are differential contributions from D_2 and D_3 receptors. An alternative mechanism potentially involves the disinhibition of the NAcbS via $D_{2/3}$ receptor-mediated inhibition of medium spiny GABA-ergic neurons in the NAcbC (Mizuno et al. 2007). This hypothesis is supported by evidence that dopamine inputs to the core and shell operate in a functionally opposed manner to regulate impulsivity (Besson et al. 2010; Diergaarde et al. 2008; Sesia et al. 2008) and that selective lesions of the NAcbC augment the effects of stimulant drugs on impulsivity in the 5-CSRTT (Murphy et al. 2008). Thus, the more pronounced effect of intra-NAcbC quinpirole on impulsivity in HI rats suggests the presence of underlying abnormalities in the NAcbS of these animals. Consistent with this notion $D_{2/3}$ receptors are significantly decreased in the NAcbS, but not NAcbC of HI rats compared with LI rats (Jupp et al. 2013). However, the precise mechanism underlying the control of NAcbS activity and output by dopamine receptors in the NAcbC of hyperimpulsive animals will require further investigation.

Neural basis of locomotor hyperactivity

While there is evidence of mediation by both the NAcbC as well as the NAcbS in the modulation of locomotor

hyperactivity by $D_{2/3}$ agents (Dreher and Jackson 1989; Gong et al. 1999; Phillips et al. 1995; Plaznick et al. 1989), the NAcS has been shown to be preferentially implicated (Heidbreder and Feldon 1998; Swanson et al. 1997). In the present study, HI and LI rats, selected according to their impulsivity response in the 5-CSRTT, but with no differences in spontaneous locomotor activity (Molander et al. 2011) exhibited differential locomotor responses following intra NAcC vs NAcS quinpirole infusions. Intra-NAcS quinpirole infusions enhanced locomotor activity in HI rats compared with both the effects of NAcC infusions and with effects in LI rats. The enhanced response by quinpirole infusion into NAcS of HI rats is in accordance with the results obtained in another selected strain of rats, the Roman high avoidance rats (RHA), which also exhibits high impulsivity as measured using the 5-CSRTT (Moreno et al. 2010). The RHA rats showed a larger increase in DA efflux in the NAcS compared to the core following acute administration of stimulants such as cocaine and D-amphetamine compared to the Roman low avoidance strain and in accordance with their enhanced locomotor response (Lecca et al. 2004). These findings are consistent with evidence that dopamine release is increased in the NAcS of HI rats in the 5-CSRTT (Diergaarde et al. 2008), an effect that may be driven by decreased presynaptic $D_{2/3}$ receptors in this region (Jupp et al. 2013).

Psychopathological implications

The greater sensitivity of HI rats to the locomotor effects of $D_{2/3}$ agonists infused into NAcS is consistent with the enhanced self-administration of cocaine and nicotine in these animals, as well as in RHA rats (Dalley et al. 2007; Diergaarde et al. 2008; Fattore et al. 2009; Giorgi et al. 2007); and substantial evidence that DA-ergic projections to the NAcS mediate the reinforcing properties of psychostimulants (Bardo 1998; Heidbreder et al. 2005; Wise 1998; for review Di Chiara 2002).

The present study also suggests that the behavioural responses of impulsivity and locomotion to $D_{2/3}$ stimulation in the NAc may be differentiated according to the site of action, DA receptor modulation and impulsivity trait. Whereas the shell sub-region in the HI rats is hypothetically relatively more sensitive to the locomotor effects of activation of D_3 receptors, the core sub-region in the HI is more sensitive to impulsivity resulting from D_2 receptor activation by quinpirole infusion. Moreover, infusion of the selective D_3 receptor antagonist nafadotride into the NAcS, reduced the quinpirole-induced locomotor response in HI rats, but was ineffective in blocking the quinpirole-induced increase in impulsive responding in the NAcC. These results support previous evidence that $D_{2/3}$ receptor dysfunction and disrupted control between the NAc sub-

regions leads to impulsive behaviour. As well as contributing to an understanding of the neurobiological mechanisms underlying impulsive traits possibly relevant to drug abuse (Dalley et al. 2011) and schizophrenia (Natesan et al. 2011), the present findings indicate possible mechanisms by which hyperactivity and impulsivity may be manifested as distinct symptoms in ADHD, modulated by $D_{2/3}$ receptors in the nucleus accumbens.

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